Influenza Vaccination in Subjects With α_1-Antitrypsin Deficiency*

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Background: **Influenza vaccination is recommended for all subjects with COPD, including α_1-antitrypsin deficiency (AATD), but immunization practices are below US national goals. Influenza vaccination practices and their relation to respiratory outcomes in AATD are unknown.**

Methods: **Nine hundred thirty-nine subjects with AATD were followed up prospectively by monthly telephone interviews during the 2003 to 2004 influenza season. Vaccination status, exacerbation rates, and health-care utilization were documented. Residence zip codes were used to group subjects as living in high or low influenza-like illness (ILI) prevalence areas according to published Centers for Disease Control and Prevention data for the same influenza season.**

Results: **Overall, 81.6% of subjects received influenza vaccination, with no differences noted by gender, age (median age 52 years), Global Initiative for Chronic Obstructive Lung Disease stage, or ILI prevalence area. No significant differences were noted in the overall acute exacerbation rates using two different criteria between vaccinated and unvaccinated subjects (mean, 1.5 ± 1 exacerbations per subject). Similarly, no differences were noted in either the severity of exacerbations or the monthly exacerbation rates between the two groups. Unvaccinated subjects had more unscheduled physician visits than vaccinated subjects, but there were no significant differences in scheduled visits, emergency department visits, or hospitalizations between the two groups. Older age (> 60 years) or residence in a high ILI prevalence area had no effect on outcomes.**

Conclusion: **Subjects with AATD in the United States receive adequate influenza vaccination regardless of age. However, we did not observe a significant impact of the vaccination on disease exacerbations and other respiratory outcomes during the 2003 to 2004 influenza season.**

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Key words: α_1-antitrypsin deficiency; influenza vaccines; outcome assessment (health care); pulmonary disease, chronic obstructive

Abbreviations: AATD = α_1-antitrypsin deficiency; ACCP = American College of Chest Physicians; CDC = Centers for Disease Control and Prevention; ED = emergency department; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ILI = influenza-like illness

Influenza virus infections result in substantial annual morbidity and mortality, imposing a great financial burden on the health-care system.[1] In subjects at increased risk for influenza-related complications, such as the elderly, young children, and subjects with certain underlying chronic medical conditions,[2] influenza vaccination has been shown to decrease influenza infection rates, influenza-related upper respiratory tract illness, physician visits, hospitalizations, and deaths.[3–5] Despite this, vaccination rates among these high-risk groups are well below US national goals.[6]

Current guidelines recommend influenza vaccination for all subjects with COPD[7]; however, there have been only a few randomized studies[8–14] that have directly assessed the efficacy of the vaccine in this population. Viral infections (including influenza) can trigger acute disease exacerbations,[15,16] which are major contributors to COPD-related morbidity and mortality.[17,18] In a small randomized trial[8] with 55 subjects, influenza vaccination significantly reduced the rate of COPD exacerbations; while in another randomized, double-blinded, placebo-controlled trial[13] with 125 patients, the vaccine reduced influenza-

related acute respiratory illness but not total exacerbation rates. Furthermore, the results of those trials probably cannot be extrapolated to younger subjects, such as those with α_1-antitrypsin deficiency (AATD), who have been shown to have COPD diagnosed at the age of 45 ± 9 years.[19] For example, in a prospective cohort study[11] of 1,696 patients with asthma and COPD, beneficial effects of influenza vaccination on deaths, pneumonia rate, and hospitalizations were observed in those > 65 years old, with no evidence for effectiveness of the vaccine in patients aged < 65 years.

Although no specific studies of vaccine efficacy have been conducted in subjects with AATD, current AATD standards of care guidelines recommend preventive influenza vaccination for subjects with AATD and documented lung disease.[20] The current study evaluates influenza vaccination practices and its impact on disease exacerbations and health-care utilization in a large cohort of subjects with AATD in the United States during the 2003 to 2004 influenza season.

Materials and Methods

Subjects and Enrollment

All participants were members of AlphaNet (Miami, FL), a not-for-profit health management company that coordinates services for subjects with AATD, including the organization and distribution of human α_1 proteinase inhibitor. Infusions of human-derived purified α_1-antitrypsin (augmentation therapy) is currently indicated for all subjects with AATD who have an α_1-antitrypsin level < 11 μmol/L and presence of obstructive lung disease, particularly with a percentage of predicted post-bronchodilation FEV_1 between 30% and 65% (recommendation level II-2).[20] The population studied also included subjects with both milder and more severe lung disease because guidelines also recommend treating subjects with normal or nearly normal pulmonary function if they have a rapid decline in lung function (> 120 mL/yr) and to keep on treating subjects with very poor lung function if already treated (both recommended as level II-2).[20] Therefore, the studied population included only AATD subjects with lung disease and did not include asymptomatic subjects with normal lung function or subjects who may have liver disease as the sole manifestation their AATD.

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The recruitment and data collection process has been previously reported.[19] Briefly, participants geographically distributed throughout the United States received a study invitation letter. Interested subjects reviewed and discussed additional study information and an informed consent document with their disease management coordinators. Those who agreed to participate mailed the signed consent forms directly to the investigators for official enrollment. The University of Miami Institutional Review Board approved the protocol and the enrollment process.

Trained disease management coordinators performed monthly telephone interviews to collect data on vaccinations, exacerbations, and health-care utilization (mainly hospitalization, emergency department [ED] visits, scheduled and unscheduled outpatient visits, ICU admissions, and use of mechanical ventilation). Survey results were directly entered at the time of collection in a secure database via an encrypted Web-based front end. Participants were requested to send, if available, a copy of a nonstandardized spirometry test result to assess their COPD stage using the FEV_1 as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[7] This study focused on the influenza season that started on week 40 of 2003 and ended on week 20 of 2004.[21] After excluding subjects who had lung transplantation, 939 subjects completed all monthly surveys during the flu season and were included in this analysis.

Exacerbations

We used two different definitions of COPD exacerbations: the criterion proposed by Rodriguez-Roisin[22] for the American College of Chest Physicians (ACCP), and the criterion based on symptoms described by Anthonisen et al.[23] Since two or more consecutive monthly surveys with positive exacerbation criteria could represent either one or more separate episodes, we clustered exacerbations depending on the total number of reported sick days.

Influenza Regions

We utilized Centers for Disease Control and Prevention (CDC) data on national influenza activity[21] to assign each subject into nine different regions based on their area of residency (zip codes): New England (region 1), Mid-Atlantic (region 2), East North Central (region 3), West North Central (region 4), South Atlantic (region 5), East South Central (region 6), West South Central (region 7), Mountain (region 8), and Pacific (region 9). Since the median percentage of visits for influenza-like illness (ILI) for all these regions was 2.09% in the present study, we used this value as the cut-off point to classify subjects as living in a high (regions 3, 5, 7, and 9) or low ILI prevalence (regions 1, 2, 4, 6, and 8) areas.

Statistical Analysis

Data were analyzed using stataistical software (SAS version 9.1.3 for Windows; SAS Institute; Cary, NC). Descriptive statistics are displayed as the mean and SD, or percentage. Differences between groups were tested using the Mann-Whitney *U* test or χ^2 test, depending on the nature of the variables; $p < 0.05$ was taken as statistically significant.

Results

Population Characteristics and Vaccination Practices in Subjects With AATD

Mean age of the 939 AATD subjects at the beginning of the influenza season 2003 to 2004 was 54.5 ± 9.6

years (median, 52 years), and 52% were male. Spirometry results performed during year 2003 were available from 641 subjects (68%). Mean FEV_1 was 1.24 ± 0.6 L, with 162 subjects (25.3%) and 355 subjects (55.4%) having stage III and stage IV COPD, respectively. All participants were receiving α_1-antitrypsin augmentation therapy during the studied period. Subjects residing in high (n = 487) or low (n = 452) ILI incidence areas had similar demographic and clinical characteristics (not shown).

Overall, 766 subjects (81.6%) reported receiving influenza vaccination for the influenza season studied. Age, gender, GOLD stage, comorbidities, or presence of chronic bronchitis did not affect vaccination status (Table 1). Similarly, the proportion of vaccinated subjects did not differ whether the residents lived in a high or low influenza incidence region (81.5% and 81.6%, respectively). There were no significant differences between unvaccinated and vaccinated subjects in the use of short-acting β-agonists (80.5% and 80.7%), long-acting β-agonists (59.1% and 61.7%), inhaled corticosteroids (65.8% and 66.7%), systemic steroids (4.9% and 5.8%), and oxygen therapy (42.0% and 48.1%). The unvaccinated group used more theophylline (23.1% vs 16.5%, p = 0.04) and fewer short-acting anticholinergics (54.2% vs 64.2%, p = 0.02).

Exacerbations During the 2003 to 2004 Influenza Season

The cohort experienced a total of 1,450 exacerbations by ACCP criteria and 1,439 exacerbations by symptoms criteria, representing 1.55 ± 0.9 exacerbations and 1.53 ± 0.9 exacerbations per subject during the influenza season, respectively. By ACCP criteria, 193 exacerbations (13.3%) were mild, 1,078 exacerbations (74.3%) were moderate, and 179 exacerbations (12.3%) were severe. By symptom criteria, 299 exacerbations (20.8%) were mild, 392 exacerbations (27.2%) were moderate, and 748 exacerbations (52%) were severe. Residents of high ILI incidence areas had more exacerbations than residents of low ILI incidence areas by both ACCP (1.64 vs 1.44, p = 0.0013) and symp-

Table 1—*Vaccination Status According to Demographic and Clinical Characteristics of the Studied Population*

Characteristics	Total, No.	Unvaccinated (n = 173), %	Vaccinated (n = 766), %	p Value
Age group, yr				0.11
34–50	301	21.8	78.2	
> 50–60	365	16.5	83.5	
> 60	273	16.0	83.9	
Gender				0.29
Male	496	17.0	82.9	
Female	443	19.7	80.3	
GOLD stage*				0.64
I–II	124	14.5	85.5	
III	162	18.5	81.5	
IV	355	16.1	83.9	
Not staged	298	22.8	77.2	
Comorbidities†				0.91
0–1	645	17.7	82.2	
≥ 2	294	18.1	81.9	
Lives with children				0.89
Yes	186	19.6	80.4	
No	753	17.6	82.4	
History of tobacco use				0.87
Yes	769	17.8	82.1	
No	170	18.4	81.6	
Actively working				0.66
Yes	323	18.1	81.9	
No	616	17.9	82.1	
Alcohol consumption				0.49
Never	284	16.5	83.5	
< 1 drink/wk	347	20.1	79.9	
> 1 drink/wk	308	17.6	82.4	
Chronic bronchitis				0.39
Yes	267	19.8	80.2	
No	672	17.2	82.8	

*A total of 641 subjects had spirometry results available.

†Comorbidities evaluated were coronary artery disease, congestive heart failure, hypertension, diabetes mellitus, vascular problems (peripheral vascular disease and cerebrovascular accidents), peptic ulcer disease, connective tissue diseases, chronic renal problems, and sinus allergies.

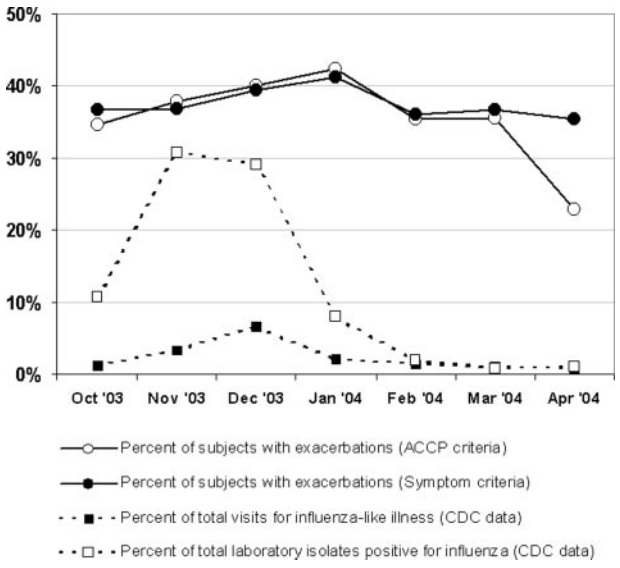

FIGURE 1. Comparison of COPD exacerbation rates in the study cohort during the influenza season 2003 to 2004 (solid line) with data on reported influenza-like illness supplied by the CDC (dashed line).[22]

toms (1.60 vs 1.46, p = 0.02) criteria. Total exacerbations by both criteria peaked in January, later than the peaks reported by the CDC for ILI and influenza isolation by culture (Fig 1). In general, the monthly variation of exacerbation rates did not vary significantly throughout the influenza season.

Influence of Influenza Vaccination on COPD Exacerbation

No significant differences were noted in the overall exacerbation rates by either criterion between the vaccinated and unvaccinated groups during the studied influenza season (Table 2). Similarly, no differences were noted on either the severity of exacerbations (Fig 2, *left*, *A*) or the monthly exacerbation rates between the two groups (Fig 2, *right*, *B*).

Influence of Influenza Vaccination on Health-Care Utilization

Unvaccinated subjects experienced more unscheduled physician visits than vaccinated subjects, but there were no significant differences in scheduled visits, ED visits, or hospitalizations between the

Table 2—*Exacerbation Rates and Health-Care Utilization Among Vaccinated and Unvaccinated Subjects With AATD During the 2003 to 2004 Influenza Season**

Variables	Unvaccinated	Vaccinated	p Value
All subjects, No.	173	766	
Exacerbations			
ACCP criteria	1.47 ± 1.0	1.56 ± 0.9	0.24
Symptom criteria	1.53 ± 1.0	1.53 ± 0.9	0.94
Health services utilization			
ED visits	0.33 ± 0.9	0.28 ± 0.8	0.99
Hospitalizations	0.2 ± 0.6	0.17 ± 0.5	0.68
Scheduled outpatient visits	3.28 ± 3.4	3.3 ± 3.2	0.32
Unscheduled outpatient visits	1.79 ± 3.6	1.33 ± 3.0	0.04
ICU admissions	0.07 ± 0.3	0.02 ± 0.2	0.01
Subjects aged > 60 yr, No.	42	220	
Exacerbations			
ACCP criteria	1.24 ± 0.9	1.55 ± 0.9	0.05
Symptom criteria	1.33 ± 0.9	1.46 ± 0.9	0.41
Health services utilization			
ED visits	0.60 ± 1.2	0.32 ± 0.9	0.08
Hospitalizations	0.19 ± 0.6	0.25 ± 0.6	0.38
Scheduled outpatient visits	4.24 ± 3.6	3.62 ± 3.5	0.24
Unscheduled outpatient visits	2.55 ± 4.8	1.59 ± 4.4	0.02
ICU admissions	0.10 ± 0.3	0.03 ± 0.1	0.15
Residents of high ILI incidence areas, No.	90	397	
Exacerbations			
ACCP criteria	1.52 ± 0.9	1.66 ± 0.9	0.17
Symptom criteria	1.67 ± 1.0	1.58 ± 0.9	0.42
Health services utilization			
ED visits	0.39 ± 0.9	0.31 ± 0.8	0.82
Hospitalizations	0.24 ± 0.7	0.20 ± 0.6	0.86
Scheduled outpatient visits	4.03 ± 3.7	3.51 ± 3.5	0.49
Unscheduled outpatient visits	2.12 ± 4.1	1.52 ± 3.5	0.17
ICU admissions	0.07 ± 0.3	0.02 ± 0.1	0.11

*Data are presented as mean ± SD unless otherwise indicated.

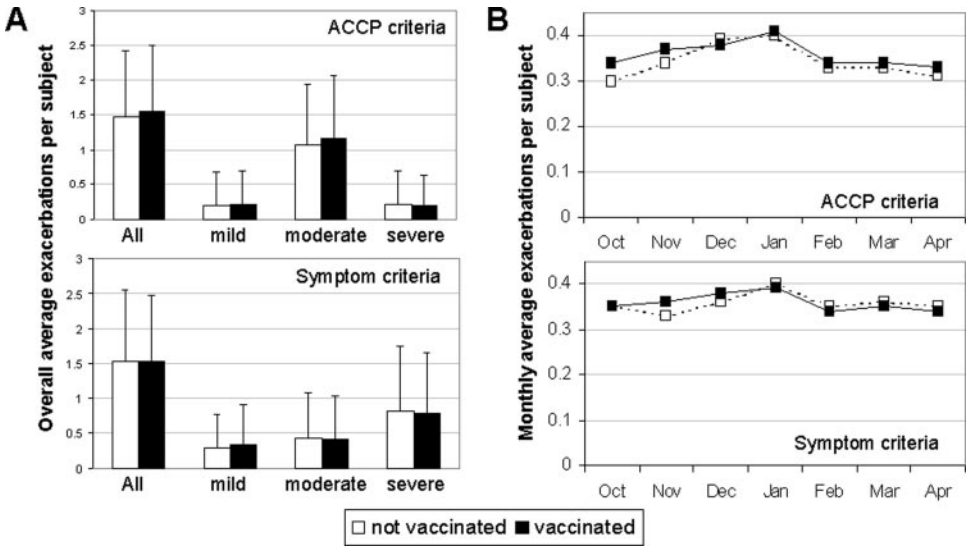

FIGURE 2. Comparison of exacerbation rates and severity among vaccinated and unvaccinated subjects with AATD during the 2003 to 2004 influenza season in the United States. *Left*, *A*: Comparison of COPD exacerbation severity using two different exacerbation criteria. *Right*, *B*: Monthly COPD exacerbation rates in the two groups according to different exacerbation criteria.

two groups (Table 2). The small number of recorded ICU admissions (12 in the unvaccinated group, and 17 in the vaccinated group) or deaths (5 in the unvaccinated group, and 9 in the vaccinated group) precludes drawing significant conclusions in this regard. We could not obtain information about the cause of death in one third of cases, so we could not assess either if respiratory-related mortality was influenced by vaccination. The total number of sick days for respiratory illness experienced per subject during the influenza season was also similar (21.9 ± 20.8 days for unvaccinated subjects, and 21.2 ± 19.6 days for vaccinated subjects, $p = 0.6$).

Since influenza vaccination appears to be more effective in elderly populations,[11] we analyzed separately subjects > 60 years old (n = 262) and did not observe any differences in exacerbation rates (Table 2). Again, in this group, unvaccinated subjects had more unscheduled physician visits but did not differ in the other health-care utilization parameters. Finally, we analyzed the effect of influenza vaccination in residents of high ILI incidence areas, not only because of their higher exacerbation rates, but also because they had more scheduled physician visits (3.6 ± 3.5 visits vs 2.9 ± 2.8 visits, $p = 0.002$), unscheduled physician visits (1.6 ± 3.6 visits vs 1.1 ± 2.5 visits , $p = 0.01$), and higher number of sick days due to respiratory illness (23.0 ± 19.2 days vs 19.5 ± 18.7 days, $p = 0.001$) compared with residents of low ILI incidence areas. We did not observe differences in exacerbation rates or health-care utilization between unvaccinated and vaccinated residents of high ILI incidence areas.

DISCUSSION

Our study aimed to evaluate vaccination practices and their effects on outcomes as they are currently practiced in the community. We found that > 80% of subjects in our cohort of subjects with lung disease and AATD received adequate influenza vaccination during the season studied, and this was independent of disease severity, age, or location. This contrasts significantly with the suboptimal overall vaccination rates reported for subjects at risk.[6,24] Specifically for the 2003 to 2004 influenza season, the reported coverage for high-risk populations was 34.6% for persons < 65 years old and 64.6% for persons > 65 years old.[2] Specific data on influenza vaccination coverage in COPD subjects are scarce because these subjects are also included in the older age group. In a Spanish cohort, the influenza vaccination rate in COPD subjects was 62%.[25] The high vaccination rates observed in our cohort may reflect a combination of increased disease management awareness by motivated individuals (reflected in their willingness to participate in this project), the effect of receiving close follow-ups as part of a health management network (AlphaNet), and/or an enhanced precaution by physicians treating a genetic disease associated with a more accelerated decline in lung function. Universal vaccination through patient and physician education is one of the goals of the AlphaNet Disease Management Program, which was not launched at the time the data presented here were collected.

An important observation of our study is that the group who received the vaccine did not have lower

exacerbation rates or decreased health-care utilization rates. If we assume that unvaccinated subjects have milder disease with less baseline exacerbation rates or live in areas with low ILI prevalence, this could be viewed as an expected finding. However, we did not observe worse lung function or a higher likelihood of living in high ILI prevalence areas in the vaccinated group. Furthermore, we did not observe differences among AATD subjects living in high ILI incidence areas. In a metaanalysis[26] of placebo-controlled randomized studies in subjects with COPD, vaccinated individuals experience a reduction in "late" exacerbations occurring ≥ 3 weeks after vaccination. From these randomized studies, we can infer several reasons why improved health outcomes were not observed in our cohort. First, it appears that most of the vaccine benefits are due to a reduction in influenza complications among the elderly as opposed to younger population with lung disease.[11] Since the average age in our cohort is approximately 10 years younger than the age of usual COPD cohorts, this may be an important factor. Second, the effects of the vaccine are mainly due to a reduction in influenza-related acute respiratory illness.[13] Particularly, for the studied influenza season (2003 to 2004), the predominant circulating influenza A virus strain was antigenically different from the vaccine strain and, consequently, this season was characterized by an early onset of influenza activity, more severe illness, and reduced overall effectiveness of the vaccine.[21] However, a case-control study[27] conducted by the CDC and the Colorado Department of Public Health and Environment in persons aged 50 to 64 years during the same 2003 to 2004 season concluded that the effectiveness of the vaccine was 52% for individuals without a high-risk condition and 38% for individuals at high risk. Although the overall vaccine effectiveness was reduced, partial protection from the vaccine should have impacted COPD exacerbation rates in our large cohort. Assuming that vaccination reduces COPD exacerbation rates by 37%,[26] our large cohort has $> 80\%$ power to detect a 15% reduction in exacerbation rate that theoretically would result from the less effective from 2003 to 2004 vaccine. Laboratory confirmation of influenza viral infection and serologic response to vaccination would have strengthened our observations.

We are not aware of prior studies addressing vaccination rates and/or the effect of influenza vaccination in subjects with AATD. This group deserves particular analysis for several reasons. As mentioned before, it is less clear if younger individuals with lung disease benefit from influenza vaccination as much as older individuals.[11] As in regular COPD and in agreement with observations done in the United Kingdom,[28] we found that exacerbations in subjects with AATD in the United States are more frequent during the winter months, which suggests a relation to viral infections. Accordingly, the lack of influenza vaccination effect in our cohort suggests that other, noninfluenza viruses may play an important role in COPD exacerbation rates. This hypothesis will require further studying.

The strengths of our study include the close follow-up of a large cohort of subjects with AATD using strict exacerbation definitions with two widely recognized criteria. The AlphaNet cohort is comprised of subjects receiving specific α_1-antitrypsin augmentation therapy. Although current guidelines recommend augmentation therapy for all AATD subjects with documented decline in lung function, we are aware that our cohort may represent the sickest subjects because individuals with milder disease more likely may not receive this therapy or be undiagnosed. Nevertheless, this cohort probably is the group that may mostly benefit from an effective vaccine.

In conclusion, influenza vaccination rates were high in subjects with AATD, but vaccination did not translate into decrease of COPD exacerbation rates or decreased health-care utilization during the 2003 to 2004 influenza season. However, we continue to advocate influenza vaccination in this population until further studies are conducted in other influenza seasons with proven vaccine correlation with circulating viral strains.

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